Acta Cryst. (1982). B**38**, 1508–1513

Neutron Diffraction at 15 K and *ab initio* Molecular-Orbital Studies of the Structure of *N*,*N*′-Diformohydrazide

By G. A. Jeffrey and J. R. Ruble

Department of Crystallography, University of Pittsburgh, Pittsburgh, PA 15260, *USA*

R. K. McMullan

Department of Chemistry, Brookhaven National Laboratory, Upton, NY 11973, *USA*

and D. J. DeFrees and J. A. Pople

Department of Chemistry, Carnegie–Mellon University, Pittsburgh, PA 15213, *USA*

(*Received* 17 *July* 1981; *accepted* 2 *December* 1981)

Abstract

The crystal structure of *N*,*N*′-diformohydrazide (1,2-hydrazinedicarboxaldehyde), $C_2H_4N_2O_2$, has been refined using single-crystal neutron diffraction data measured at 15 K [$P2_1/c$, $Z = 2$, $a = 3{\cdot}4724\,(5)$, $b = 6{\cdot}1770\,(8)$, $c = 8{\cdot}939\,(1)$ Å, $\beta = 111{\cdot}92\,(1)^\circ$, $R(F) = 0{\cdot}024$, $R(F^2) = 0{\cdot}021$, $wR(F) = 0{\cdot}012$, $wR(F^2) = 0{\cdot}024$, $S = 1{\cdot}210$ for 710 reflections]. The molecular symmetry is $\bar{1}$, approximately $2/m$, with observed [thermal-motion corrected] bond lengths N—N, 1·3808 (4) [1·387]; C—N, 1·3321 (4) [1·333]; C=O, 1·2384 (4) [1·244]; C—H, 1·0997 (7) [1·113]; N—H, 1·0385 (7) [1·047] Å. *Ab initio* molecular-orbital (MO) calculations were carried out at the Hartree–Fock STO-3G level for all planar conformations of the molecule. The most stable planar conformer was that observed in the crystal. When complete *ab initio* MO geometry optimization of the observed conformer was calculated at the HF/3-21G level, the planar, $2/m$ conformation was not an energy minimum in the theoretical potential-energy surface. The minimum-energy conformation, calculated for the isolated molecule, is 5·4 kJ mol^{-1} lower and has symmetry 2, as does hydrazine, with a C—N—N—C torsion angle of +84·5°. The molecules in the crystal are hydrogen-bonded in the $(10\bar{2})$ planes, which are separated by 3·184 (5) Å. The intermolecular (N)H···O hydrogen-bond lengths are 1·7543 (7) Å. There is a weak intramolecular (N)H···O interaction at 2·3867 (8) Å. A thermal-motion analysis gave a good rigid-body-motion fit for the non-hydrogen atoms, with $\langle \text{r.m.s.}\ \Delta U_{ij}\rangle = 0{\cdot}0005$ Å^2, $\sigma(U_{ij}) = 0{\cdot}0006$ Å^2.

Introduction

The crystal structure of *N*,*N*′-diformohydrazide (1,2-hydrazinedicarboxaldehyde) was determined by X-ray diffraction at room temperature by Tomiie, Koo & Nitta (1958). This early analysis was remarkable in that it included the location of the H atoms and an analysis of the valence-electron distribution based on two-dimensional film data. The structure was refined with diffractometer data taken at 85 K by Hope & Ottersen (1978), who later carried out a deformation electron density analysis (Hope & Ottersen, 1979). A room-temperature electron density analysis was also reported by Tanaka (1978). A deformation density analysis based on the Hope & Ottersen (1978) data has been reported (Eisenstein, 1979).

The present low-temperature neutron diffraction analysis at 15 K has been carried out to permit as close a comparison as possible with the *ab initio* calculations for the molecular geometry of the isolated molecule at rest. It is an extension of similar studies on the structures of small first-row-element molecules, which include acetamide (Jeffrey, Ruble, McMullan, DeFrees, Binkley & Pople, 1980), fluoroacetamide (Jeffrey, Ruble, McMullan, DeFrees & Pople, 1981*a*) and formamide oxime (Jeffrey, Ruble, McMullan, DeFrees & Pople, 1981*b*).

Experimental

The neutron diffraction data collection and structure refinement followed the same methods and procedures as described for formamide oxime (Jeffrey, Ruble, McMullan, DeFrees & Pople, 1981*b*), except for the information given below. The crystal data are given in Table 1. Large prismatic rods with $\{011\}$ and $\{10\bar{2}\}$ were obtained by slow evaporation of an aqueous solution. The crystal used was 2·1 × 1·5 × 1·1 mm, 3·26 mm^3, 0·00513 g, with six natural faces and one cut face $(0\bar{1}0)$. The crystal was mounted with the $[0\bar{1}1]$ direction 16° off the φ axis of the diffractometer and

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Table 1. *Crystal data for N,N′-diformohydrazide*

$C_2H_4N_2O_2$; CAS Reg. No. 628-36-4; space group $P2_1/c$; $Z = 2$.

	This work 15 K	Hope & Ottersen (1978) 85 K	Tanaka (1978) 296 K	Tomiie, Koo & Nitta (1958) 298 K	Reduced cell ($P2_1/n$)
a (Å)	3·4724 (5)	3·4829 (3)	3·5846 (7)	3·565 (2)	3·4724
b (Å)	6·1770 (8)	6·1855 (6)	6·2617 (7)	6·253 (2)	6·1770
c (Å)	8·939 (1)	8·9383 (7)	8·987 (1)	8·939 (4)	8·294
β (°)	111·92 (1)	112·06 (1)	113·05 (2)	112·5 (1)	90·94
V (Å^3)	177·87	178·46	184·40	184·10	
D_x (Mg m^{-3})	1·644	1·639	1·576	1·588	
λ_n (Å)	1·0442 (1)				

Table 2. *Final atomic parameters* ($\times 10^5$) *for N,N′-diformohydrazide*

The standard deviations are given in parentheses. $T = \exp[-2\pi^2 \sum_i^3 \sum_j^3 h_i h_j a_i^* a_j^* U_{ij}]$. Isotropic $g = 0{\cdot}052\ (2) \times 10^4$ rad^{-1}.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C	10674 (8)	21825 (4)	13888 (3)	551 (10)	450 (10)	391 (10)	26 (8)	43 (8)	−59 (8)
N	−6503 (6)	10488 (3)	333 (2)	579 (8)	500 (8)	361 (7)	63 (6)	−14 (6)	−47 (6)
O	38018 (10)	14599 (5)	26216 (4)	665 (11)	609 (13)	425 (12)	14 (9)	−54 (10)	−34 (9)
H(C)	−1945 (24)	38305 (11)	13045 (9)	2547 (30)	1269 (25)	2032 (28)	622 (24)	318 (24)	−195 (21)
H(N)	−29136 (21)	16994 (11)	−9894 (8)	1776 (25)	1722 (25)	1215 (23)	359 (22)	−60 (20)	66 (20)

was cooled at a rate of 1° min^{-1} to a temperature of $15{\cdot}0 \pm 0{\cdot}5$ K which was maintained during data collection. The lattice parameters in Table 1 were determined from $\sin^2\theta$ values of 32 reflections with $47° < 2\theta < 56°$. Neutron integrated intensities were measured for one quadrant ($h,\bar{k},\pm l$), using scan widths of $\Delta(2\theta) = 4{\cdot}80°$ for $\sin\theta/\lambda \le 0{\cdot}48$ Å^{-1} and varied according to the dispersion formula $\Delta(2\theta) = (3{\cdot}807 + 2{\cdot}711 \tan\theta)°$ for $0{\cdot}48$ Å$^{-1} < \sin\theta/\lambda < 0{\cdot}79$ Å^{-1}. The transmission factors in the absorption corrections ($\mu = 178$ m^{-1}) ranged from 0·75 to 0·86. The data for 95 symmetry-related $0kl$ reflections gave $\sum|\langle F^2\rangle - F^2|/\sum\langle F^2\rangle = 0{\cdot}011$. Of the 805 reflections measured, there were four recorded with net negative intensities which were not significantly different from zero. The initial atomic coordinates used were those of Hope & Ottersen (1978) with assumed isotropic temperature factors of 0·006 Å^2 for non-hydrogen atoms and 0·009 Å^2 for H. The refinement was by full-matrix least squares (Busing, Martin & Levy, 1962). The quantity minimized was $w(F_o^2 - F_c^2)^2$, where $w^{-1} = [\sigma_c^2 + (0{\cdot}01F_o^2)^2 + (2850/F_o^2)^2]^{1/2}$. The constant last term, which was selected so that the largest $F^2 = \sigma(F^2)$ for the glide-plane extinctions with largest I_o, was used to decrease the weight of weak reflections. The refinement used 710 unique structure amplitudes for the determination of 45 atomic parameters, a scale factor, and one isotropic extinction parameter for a type 1 crystal with a Lorentzian distribution (Becker & Coppens, 1974). There were no changes greater than $0{\cdot}05\sigma$ in the final refinement cycle. The largest feature on the final difference map was $0{\cdot}5\sigma_{(\varrho)}$ where the error

Table 3. *Experimental and theoretical molecular dimensions of N,N′-diformohydrazide*

Estimated standard deviations given in parentheses refer to the least significant figure.

	Experimental			Theoretical 3-21G	
	X-ray, 85 K	Neutron, 15 K			
	Observed	Observed	Corrected	$2/m$, C_{2h}	2, C_2
Bond lengths (Å)					
C–N	1·3316 (2)	1·3321 (4)	1·333	1·342	1·365
N–N	1·3797 (2)	1·3808 (4)	1·387	1·412	1·391
C=O	1·2380 (2)	1·2384 (4)	1·244	1·218	1·207
C–H	1·070 (18)	1·0997 (7)	1·113	1·079	1·082
N–H	1·021 (19)	1·0385 (7)	1·047	0·998	0·996
Bond angles (°)					
O–C–N	123·56 (1)	123·65 (3)	123·5	123·3	124·8
C–N–N	119·38 (1)	119·34 (2)	119·2	117·4	119·3
O–C–H(C)	121·0 (9)	123·23 (5)	123·5	123·8	123·7
N–C–H(C)	115·4 (9)	113·12 (4)	113·0	112·9	111·4
C–N–H(N)	120·7 (11)	122·14 (4)	122·0	129·3	122·2
N–H–H(N)	120·0 (11)	118·51 (4)	118·8	114·3	116·8
Torsion angles (°)					
C–N–N′–C′		180		180	84·5
N′–N–C–O		−0·30 (4)		0	8·2
O–C–N–H(N)		−179·2 (5)		180	172·9
C′–N′–N–H(N)		−1·05 (6)		0	−81·1
N′–N–C–H(C)		179·81 (5)		180	−173·3
H(N)–N–C–H(C)		0·90 (8)		0	−8·6
H(N)–N–N′–H(N′)		180		180	113·4

N pyramidization, θ_p

$$\theta_p = \cos^{-1}\left(\frac{\mathbf{V}_i . \mathbf{V}_j \times \mathbf{V}_k}{|\mathbf{V}_i| . |\mathbf{V}_j \times \mathbf{V}_k|}\right); \mathbf{V}_1 = \mathrm{N}\rightarrow\mathrm{N}', \mathbf{V}_2 = \mathrm{N}\rightarrow\mathrm{C}, \mathbf{V}_3 = \mathrm{N}\rightarrow\mathrm{H}.$$

	Experimental, neutron, 15 K	Theoretical 3-21G θ_p (calc.)	
	θ_p (obs.)	$2/m$, C_{2h}	2, C_2
$i = 1, j = 2, k = 3$	90·9°	90°	76·7°
$i = 2, j = 3, k = 1$	90·9	90	77·4
$i = 3, j = 1, k = 2$	90·9	90	77·1

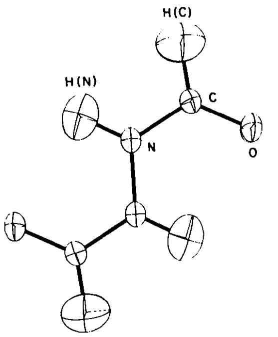

Fig. 1. Thermal ellipsoids at 95% probability (Johnson, 1976) and the atomic notation for *N,N'*-diformohydrazide at 15 K.

in p was estimated from $\sigma_{(F)}$. Extinction was minor with only six reflections having correction factors (yF_c^2) less than 0·90. The most severe was $0{\cdot}85F_c^2$ for 004. The agreement factors are $R(F) = 0{\cdot}024$, $R(F^2) = 0{\cdot}021$, $wR(F) = 0{\cdot}012$, $wR(F^2) = 0{\cdot}024$, $S = 1{\cdot}210$. The atomic parameters are given in Table 2. The molecular dimensions are given in Table 3, and the atomic notation and thermal ellipsoids are shown in Fig. 1.*

The largest differences between these atomic coordinates and those reported by Hope & Ottersen (1978) from X-ray diffraction at 85 K were 0·00023 Å for y(N), 0·00016 Å for z(C), and 0·0055 Å for z(HC). These were $12\sigma_{\text{X-ray}}$, $16\sigma_{\text{X-ray}}$ and $2\sigma_{\text{X-ray}}$, respectively.

Thermal-motion analysis

The segmented-body method of Johnson (1970) was used. An initial analysis was carried out with the five atoms of the asymmetric unit in the segments, NCO, H(C), H(N), with three joints interconnecting the segments and the stationary lattice. The calculated internal motions were 0·074 Å for the r.m.s. N—H stretch, 0·015 Å for the r.m.s. in-plane 'half-scissor' motion, 0·073 Å for the r.m.s. C—H stretch and 0·110 Å for the r.m.s. C—H in-plane 'half-scissor'. Attempts to determine the out-of-plane motion of the C—H and N—H bonds led to singularities. These internal motions were then subtracted from the r.m.s. displacements prior to the final segmented-body analysis. The model used for the rigid-body motion had one segment with a flexible joint from the center of symmetry to the stationary lattice. This is equivalent to the Schomaker & Trueblood (1968) non-hydrogen-atom rigid-body refinement. The motion with reference to **a**, **b**, **c*** is given below.

		l_1	l_2	l_3
T	0·068 Å	56·2°	141·9°	105·5°
	0·062	48·6	52·1	115·5
	0·054	59·8	86·4	30·5
ω	6·1°	84·6	56·1	34·4
	1·2	85·8	146·1	56·4
	1·0	6·8	89·5	96·8

The overall fit was good, $\langle \text{r.m.s. } U_{ij(\text{obs})} - U_{ij(\text{calc})} \rangle = 0{\cdot}0005$ Å^2, with $\sigma(U_{ij}) = 0{\cdot}0006$ Å^2. The N—N, C—N and C=O bond lengths were corrected for libration motion, and the C—H and N—H bond lengths for riding motion (Busing & Levy, 1964).

Discussion of the crystal structural results

As shown from the molecular dimensions given in Table 3, the molecule is close to being exactly planar. The largest deviation from planarity is that of H(N), which is 0·0102 Å out of the least-squares plane. This corresponds to 1° of pyramidization of the N atom, see Table 3, as compared with 50° in hydrazine. Isomerism in the planar conformation is possible, due to the multiple character of the N—N and C—N bonds. The observed centrosymmetric *cis–trans* isomer (1) is

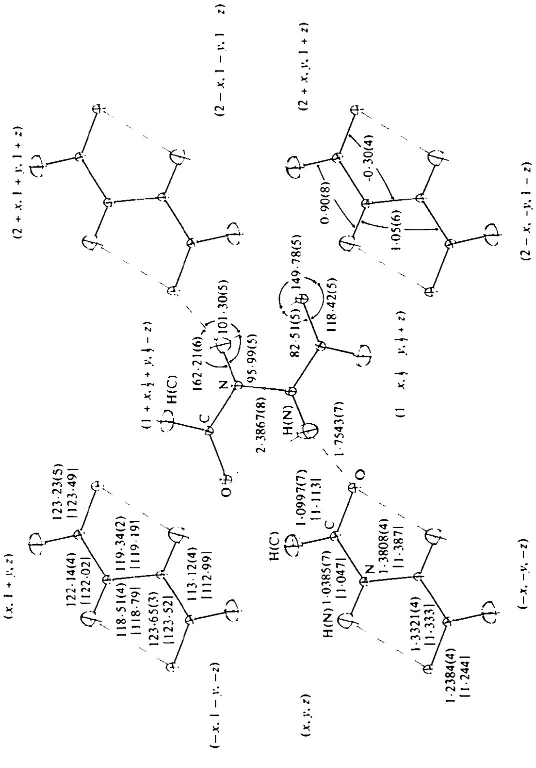

Fig. 2. Hydrogen bonding in the crystal structure of *N,N'*-diformohydrazide. Values in square brackets are bond lengths (Å) and bond angles (°) corrected for thermal motion. The plane of the diagram is (10$\bar{2}$).

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* Tables of observed and calculated structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36569 (6 pp.). Copes may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

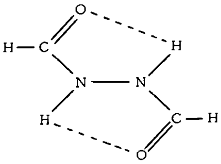
stabilized by the two intramolecular hydrogen-bond interactions between H(N) and O at 2·3867 (8) Å.

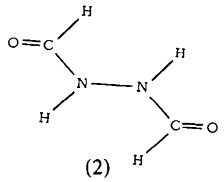
The uncorrected molecular dimensions are in excellent agreement with those measured by X-ray diffraction at 85 K (Hope & Ottersen, 1978). For the non-hydrogen atoms, the largest difference was 0·0011 Å (5σ, X-ray) in bond length. The neutron diffraction C—H and N—H bond lengths were longer than the X-ray values by 1·7σ and 0·9σ, respectively, of the X-ray data.

The hydrogen bonding is shown in Fig. 2. It is simple, being entirely in the plane of the molecules, which is the (10$\bar{2}$) plane of the crystal. The separation between these hydrogen-bonded molecular planes is 3·184 (5) Å. The intermolecular N—H···O=C hydrogen-bond length of 1·7543 (7) Å is one of the shorter neutron diffraction values hitherto reported for this type of hydrogen bond. The N—H···O angle is 162·21 (6)°. Comparable short N—H···O=C bond lengths are from the imidazole N—H bond in the crystal structures of L-histidine, 1·720 Å (Lehmann, Koetzle & Hamilton, 1972), and L-histidine hydrochloride monohydrate, 1·580 Å (Fuess, Hohlwein & Mason, 1977).

Ab initio molecular-orbital calculations

Ab initio molecular-orbital theory was used at the Hartree–Fock (HF) level with the STO-3G and 3-21G basis sets using the *GAUSSIAN*-80 program (Binkley, Whiteside, Krishnan, Seeger, DeFrees, Schlegel, Topiol, Kahn & Pople, 1981). The minimum-energy structures were calculated within specified symmetry constraints. In an initial study, the five possible planar structures, (1) to (5), were examined at the HF/STO-3G level. Energies are given in Table 4. Structure (1), the one found in the crystal, is found to be the most stable of these. Its higher stability may reasonably be associated with the two intramolecular NH···O hydrogen bonds.


(1)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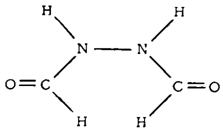
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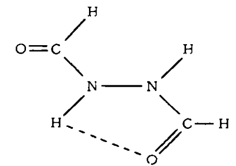
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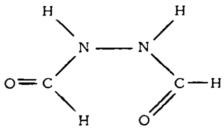
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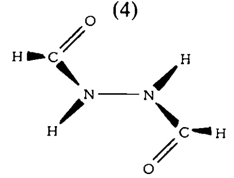

(6)

In the next stage, the geometry of structure (1) was optimized at the HF/3-21G level, leading to the structural parameters and energy given in Tables 3 and 4. However, this planar structure does not correspond to a local minimum on the full 3-21G potential surface. Release of the planar constraint leads to structure (6), with 2 (C_2) symmetry having an energy 5·4 kJ mol^{-1} (1·3 kcal mol^{-1}) below that of (1).

Structure (6) has a C—N—N—C dihedral angle of 84·5° and N pyramidization of 13°. The structural parameters and energy for this structure are also given in Tables 3 and 4. This theoretical prediction that the isolated molecule of diformohydrazide is non-planar is related to the general tendency of the $>$N—N$<$ bonds to be non-coplanar. In hydrazine itself, the non-planarity is ascribed to the net antibonding effect of the 4π electrons in the planar conformation. In diformohydrazide, the formyl groups delocalize the antibonding π electrons, thereby reducing the destabilization of the planar form. In addition, the planar geometry is more favorable for the intramolecular hydrogen-bond formation, since it permits an (N)H···O(C) distance of 2·28 Å, *versus* 3·01 Å in the non-planar form (6). As a consequence of both these effects, the energy difference between the non-planar and planar conformations

Table 4. HF/STO-3G *and* HF/3-21G *energies for planar diformohydrazide rotamers*

		Total energy (hartrees)*		Relative energy			
				kcal mol^{-1}		kJ mol^{-1}	
Structure	Point group	HF/STO-3G	HF/3-21G	STO-3G	3-21G	STO-3G	3-21G
(3)	*mm* (C_{2v})	−332·18952		6·7		28·2	
(5)	*m* (C_s)	−332·19316		4·5		18·7	
(2)	2/*m* (C_{2h})	−332·19481		3·4		14·3	
(4)	*m* (C_s)	−332·19696		2·1		8·7	
(1)	2/*m* (C_{2h})	−332·20027	−334·76796	0·0	1·3	0·0	5·3
(6)	2 (C_2)		−334·76999		0·0		0·0

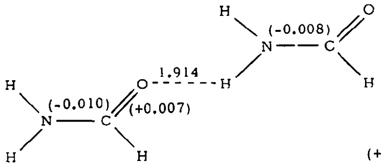
* 1 hartree = 4·35916 × 10^{-18} J.

about the N—N bond is much lower in diformohydrazide than the 108 kJ mol^{-1} (26 kcal mol^{-1}) calculated (HF/3-21G) for hydrazine (Whiteside, Binkley, Krishnan, Frisch, DeFrees, Schlegel & Pople, 1981).

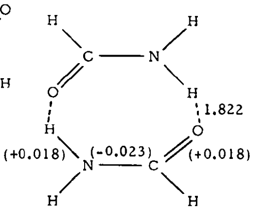
Comparison of theoretical and experimental results

This is the second example in the series of molecules which we have studied in which the theoretical minimum-energy conformation for the isolated molecule at rest differs from that observed in the crystal. The other example is that of acetamide in its rhombohedral crystal structure (Jeffrey *et al.*, 1980). While these differences were not predicted, they do not appear unreasonable, in retrospect.

A detailed comparison of the bond-length differences between the observed diformohydrazide molecule and those calculated for the same planar conformation is shown in Table 5. As in the discussion of the structures of acetamide and fluoroacetamide (Jeffrey *et al.*, 1981*a*,*b*), the errors arising from approximations in the theory were estimated from a comparison between the results of HF/3-21G and higher-order calculations for simpler molecules with the same bonds. The corrections for the effect of hydrogen bonding were taken from HF/3-21G calculations on the formamide monomer and the dimer structures, shown in (7) and (8).



(7)



(8)

Unlike the acetamide and fluoroacetamide structure, the intermolecular hydrogen bonding in this structure more closely resembles the extended formamide dimer molecule (7) than the closed dimer (8). Corrections for hydrogen bonding, from the 3-21G extended- and closed-dimer calculations, are shown in parentheses. The hydrogen bonds are longer in the extended dimer than in the closed dimer, 1·914 *versus* 1·822 Å, and the corrections are smaller. The extended-dimer corrections resulted in good agreement for the C—N bonds, but a significant difference for the C=O bonds, with the theoretical value too short. If we use the closed dimer as our model for hydrogen-bonding effects, these differences are reversed.

The differences in the observed and calculated N—N bond lengths are fully accounted for by the approximations of the theory, using planar hydrazine as the model. As with the previous studies, there are large residual discrepancies in the C—H and N—H bond lengths, which would be significantly reduced if we assume that the effects of anharmonicity and riding motion are self-cancelling and that the riding-motion corrections (Busing & Levy, 1964) alone overestimate the librational bond shortening.

Table 5. *Analysis of bond-length discrepancies* (Å)

Values in parentheses are uncorrected for riding motion.

Bond	Theory — experimental	Higher-level extrapolation† MP3/6-31G* — HF/3-21G	H-bonding dimer—monomer HF/3-21G	Residual discrepancy
N—N	+0·025	−0·027^a	–	−0·002
C—N	+0·009	−0·005^b	−0·023‡	−0·019
			−0·009§	−0·005
C=O	−0·026	+0·003^c	+0·018‡	−0·005
			+0·007§	−0·013
C—H	−0·034 (−0·021)	+0·008^d	–	−0·026 (−0·013)
N—H	−0·049 (−0·040)	+0·014^e	+0·018‡	−0·017 (−0·008)

† Whiteside *et al.* (1981): (*a*) hydrazine (planar); (*b*) methylamine; (*c*) formaldehyde; (*d*) methane; (*e*) methylamine.

‡ Formamide monomer to cyclic dimer, at HF/3-21G.

§ Formamide monomer to extended dimer, at HF/3-21G.

The neutron diffraction analysis in this research was carried out at Brookhaven National Laboratory under contract with the Department of Energy, and was supported in part by its Office of Basic Energy Sciences. We wish to thank Mr Joseph Henriques for his technical assistance. The theoretical calculations were supported by NSF Grant CHE79-01061 at Carnegie–Mellon University.

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The Structure of *S*-Adenosyl-L-homocysteine 2·5-Hydrate

BY H.-S. SHIEH* AND HELEN M. BERMAN

The Institute for Cancer Research, Fox Chase Cancer Center, 7701 *Burholme Avenue, Philadelphia, PA* 19111, *USA*

(*Received* 8 *June* 1981; *accepted* 8 *December* 1981)

Abstract

S-Adenosyl-L-homocysteine (SAH), a potent inhibitor for *S*-adenosyl-L-methionine(SAM)-dependent transmethylation reactions, crystallizes from aqueous solution: $C_{14}H_{20}N_6O_5S.2{\cdot}5H_2O$, M_r = 429·45, $C2$, a = 45·658 (3), b = 5·6790 (4), c = 15·592 (1) Å, β = 99·752 (6)°, V = 3984·42 Å^3, Z = 8, d_c = 1·43 g cm^{-3}, μ(Cu $K\alpha$) = 18·0 cm^{-1}, $F(000)$ = 1816. The crystal structure was solved by a combination of systematic searches of Patterson space and superposition. Its absolute configuration was established using hkl and $\bar{h}\bar{k}\bar{l}$ reflections. The structure was refined by a block-diagonal least-squares procedure to a discrepancy factor of 0·074 for 2329 reflections with $I \geq 2{\cdot}33\sigma_I$. There are two independent SAH and five water molecules in one asymmetric unit. The two SAH molecules have different conformations with respect to both their amino acid and nucleoside portions. The crystal structure is held together by a hydrogen-bonding network that includes asymmetric base pairing, and interactions between the amino acid and ribose rings, adenine rings and symmetry-related amino acids.

Introduction

S-Adenosyl-L-homocysteine (SAH), the demethylated product of the *S*-adenosyl-L-methionine(SAM)-dependent transmethylation reactions, is also the natural inhibitor to these reactions. It was shown that SAH and SAM compete for the same enzymatic site (Baudry, Chast & Schwartz, 1973; Coward, Slisz & Wu, 1973; Borchardt, Huber & Wu, 1974). A model of the SAM–enzyme-binding complex was proposed by Zappia, Zydek-Cwick & Schlenk (1969). A similar binding site for SAH was proposed by Borchardt (1977) based on the activity studies of a series of SAH analogues. In the proposed model (Fig. 1) many parts of the SAH molecule are required for enzymatic binding. The amino acid moiety binds such that rigid spatial relationships may be maintained among the three functional groups, —S—, NH$_3^+$ and —COO$^-$. In the ribose moiety, the two —OH groups are important although the exact nature of their roles has not been elucidated. It is known that in the base portion the 6-amino group is always required for transmethylation reactions while N(3) and N(7) participate in only a few such reactions.

The purpose of the present study was to determine the configuration and conformation of SAH. The structure of SAH has not been determined, although its absolute configuration at the sulfonium center was

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* Present address: Physical Science Center, Monsanto Company, 800 N. Lindbergh Boulevard, St Louis, MO 63166, USA.

0567-7408/82/051513-05$01.00